```
=> s verapamil or 52-53-9/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L3       90094 VERAPAMIL OR 52-53-9/RN

=> s hydroxypropylmethyl cellulose
L4        6633 HYDROXYPROPYLMETHYL CELLULOSE

=> s hydroxypropylmethyl cellulose or hydroxypropylcellulose or
carboxymethylcellulose or xanthan gum or polyethylene oxide
L5       93908 HYDROXYPROPYLMETHYL CELLULOSE OR HYDROXYPROPYLCELLULOSE OR
CARBO
               XYMETHYLCELLULOSE OR XANTHAN GUM OR POLYETHYLENE OXIDE

=> s polyethylene glycol or stearic acid or dibutyl sebacate or propylene
glycol or triethyl citrate
   4 FILES SEARCHED...
L6      390146 POLYETHYLENE GLYCOL OR STEARIC ACID OR DIBUTYL SEBACATE OR
PROPY
               LENE GLYCOL OR TRIETHYL CITRATE

=> s methacrylic acid or acrylic acid
   4 FILES SEARCHED...
L7      220725 METHACRYLIC ACID OR ACRYLIC ACID

=> s silicone dioxide
L8        1194 SILICONE DIOXIDE

=> s l3 and l5 and l6 and l7 and l8
L9           3 L3 AND L5 AND L6 AND L7 AND L8

=> d l9 1-3 ab bib kwic

L9   ANSWER 1 OF 3  USPATFULL
AB     A two pulse gastrointestinal delivery system is provided. The system
       comprises a desired agent in combination with a swellable core
material,
       the core being surrounded by an inner coat of a water-insoluble or
       relatively water-insoluble coating material in which particulate
       water-insoluble material is embedded. The inner coat is additionally
       surrounded by an outer coat that contains additional amounts of the
       desired agent. When the delivery device enters the gastrointestinal
       tract, the outer coat releases the desired agent contained therein and
       disintegrates, exposing the inner coat. The particulate matter in the
       inner coat takes up liquid, thus forming channels interconnecting the
       drug-containing core with the outside of the delivery device. Through
       these channels liquid enters the core which then swells to the point at
       which the inner coat is broken. When the integrity of the inner coat is
       destroyed, the core then disintegrates, immediately releasing all or
       most of the drug at a specific site. By controlling parameters in the
       device, such as the core material, carrier material in the coating, and
       particulate matter, the location of release of both pulses of the drug
       can be carefully controlled. The invention is also directed to a method
       of using the device for the treatment of disease by the release of
drugs
       in the gastrointestinal tract in a location- and time-dependent manner.
AN     2002:205905  USPATFULL
TI     DELAYED TOTAL RELEASE TWO PULSE GASTROINTESTINAL DRUG DELIVERY SYSTEM
IN     PENHASI, ADEL, BAT YAM, ISRAEL
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FLASHNER, MOSHE, PETAH TIKVA, ISRAEL
LERNER, E. ITZHAK, PETAH TIKVA, ISRAEL
PI US 2002110593 A1 20020815
AI US 1999-325748 A1 19990604 (9)
DT Utility
FS APPLICATION
LREP DR. D. GRAESER LTD., THE POLKINGHORNS, 9003 FLORIN WAY, UPPER MARLBORO, MD, 20772
CLMN Number of Claims: 66
ECL Exemplary Claim: 1
DRWN 24 Drawing Page(s)
LN.CNT 2255
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . controlled by combinations of controlled release layers, swelling layers and coating layers. The controlled release layer is a slightly crosslinked poly(**acrylic acid**) polymer of high molecular weight admixed with a water soluble polymer. This system too suffers from the disadvantage of not. . .
SUMM . . . partially water permeable layer onto a swellable core which contains drug. The outer shell consisted of hydrogenated castor oil and **polyethylene glycol** 6000 and could control lag time by changing the thickness or the relative composition of the pressed outer layer.
DETD . . . that may be used for a sustained release layer are hydroxypropylmethylcellulose, povidone, gelatin, waxes, low methoxy pectin, pectin, lactose, starch, **silicone dioxide** and magnesium stearate.
DETD . . . polymer. Ethylcellulose NE-20 is a highly preferred polymer. Eudragit.RTM. RL.TM. is a dimethylaminoethylacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and **methacrylic acid** esters with a low content of quaternary ammonium groups. The molar ratio of the ammonium groups to the remaining neutral (meth) **acrylic acid** esters is about 1:20. This polymer corresponds to USP/NF "Ammonio Methacrylate Coplymer Type A."
DETD [0097] Eudragit.RTM. RS.TM. is an ethylmethacrylate/chlorotrimethylammon iumethyl methacrylate copolymer, a copolymer based on acrylic and **methacrylic acid** esters with a low content of quaternary ammonium groups. The molar ratio of the ammonium groups to the remaining neutral (meth)**acrylic acid** esters is 1:40. The is polymer corresponds to USP/NF "Ammonio Methacrylate Copolymer Type B."
DETD [0098] Eudragit.RTM. L.TM. is a **methacrylic acid** /methylmethacrylate or ethylacrylate copolymer, an anionic copolymer based on **methacrylic acid** and methylmethacrylate or on **methacrylic acid** and ethylacrylate. The ratio of free carboxyl groups to the ester groups is approximately 1:1. This polymer corresponds to USP/NF "**Methacrylic Acid** Copolymer Type A and Type C."
DETD . . . formaldehyde-crosslinked gelatin, glutaraldehyde- or formaldehyde-crosslinked collagen, any insoluble complex of a polysaccharide and a protein or peptide, glutaraldehyde- or formaldehyde-crosslinked **hydroxypropylcellulose**, glutaraldehyde- or formaldehyde-crosslinked hydroxyethylcellulose, glutaraldehyde- or formaldehyde-crosslinked hydroxypropylmethylcellulose, or any of the carbomers (crosslinked **acrylic acid** polymers). Specific examples of the water-insoluble carrier include, but are not limited to, Eudragit.RTM. RL.TM., Eudragit.RTM. RS.TM., ethylcellulose, shellac, and. . .
DETD . . . a hardness enhancer. Useful hardness enhancers include, but are

not limited to, microcrystalline cellulose (Emcocel.RTM.), starch, polyvinylpyrrolidone, low molecular weight **hydroxypropylcellulose**, and low molecular weight hydroxypropylmethylcellulose. In a preferred embodiment, microcrystalline cellulose (MCC) is the hardness enhancer. MCC is preferably present. . .

DETD . . . Crosprovidone, microcrystalline cellulose, starch, or microcrystalline starch or any combination thereof. Alternate core materials include, but are not limited to, **carboxymethylcellulose**, calcium alginate, cross-linked guar gum, cross-linked polysaccharide, cross-linked vegetable gum, cross-linked hydrophilic polymer, alginic acid, sodium alginate, carrageenan, or any.

. .

DETD . . . crospovidone from 5-15%, most preferably 10-12%, the drug from 0. 1-40%, most preferably 2-10%, microcrystalline cellulose 20-60%, most preferably 45-55%, **silicone dioxide** (as an optional glidant) 0-2%, most preferably 0.5-1%, Eudragit.RTM. S or povidone (as an optional granulation binder) 0-3%, most preferably. . .

DETD . . . metoprolol, and vasopril; anti-spasmodic agents such as cimetropium bromide; anti-colitis agents such as 5-aminosalicylic acid; anti-arrhythmia agents such as quinidine, **verapamil**, procainamide, and lidocaine; anti-neoplastic agents such as methotrexate, tamoxifen, cyclophosphamide, mercaptopurine, and etoposide; protein or peptide drugs such as insulin,. . . .

DETD [0183] The pyridostigmine-containing granules were mixed with 1.4 grams of **silicone dioxide**, Aerosil.RTM. R972, for 5 minutes to improve their flow properties. The mixture was transferred to a polyethylene bag to which. . .

CLM What is claimed is:

. . . wherein said water-insoluble carrier is selected from the group consisting of: a dimethylaminoethylacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and **methacrylic acid** esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth) **acrylic acid** esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and **methacrylic acid** esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth) **acrylic acid** esters is 1:40; ethylcellulose; shellac; and zein.

. . . 17. The device of claim 15, wherein said modified cellulose is selected from the group consisting of cross-linked derivatives of **hydroxypropylcellulose**, hydroxyethylcellulose, methylcellulose and **carboxymethylcellulose** and metal salts of **carboxymethylcellulose**.

. . . alginic acid; an insoluble crosslinked derivative of xantham gum, guar gum, dextran, carrageenan, tragacanth gum, locust bean gum, pectin, starch, **hydroxypropylcellulose**, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxymethyl-cellulose and alginic acid, cellulose, microcrystalline cellulose, insoluble starch and microcrystalline starch.

. . . 14, wherein said water-insoluble carrier is ethylcellulose, said water-insoluble hydrophilic particulate is calcium pectinate, and said enteric coating is a **methacrylic acid** /methylmethacrylate or ethylacrylate anionic copolymer based on i) **methacrylic acid** and methylmethacrylate or ii) on **methacrylic acid** and ethylacrylate, wherein the ratio of free carboxyl groups to the ester groups is approximately 1:1.

. . . wherein said water-insoluble carrier is selected from the group consisting of: a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and **methacrylic acid** esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth) **acrylic acid** esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and **methacrylic acid** esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth) **acrylic acid** esters is 1:40; ethylcellulose; shellac; and zein.

. . . 41. The method of claim 39, wherein said modified cellulose is selected from the group consisting of cross-linked derivatives of **hydroxypropylcellulose**, hydroxyethylcellulose, methylcellulose and **carboxymethylcellulose** and metal salts of **carboxymethylcellulose**.

. . . alginic acid; an insoluble crosslinked derivative of xantham gum, guar gum, dextran, carrageenan, tragacanth gum, locust bean gum, pectin, starch, **hydroxypropylcellulose**, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxymethyl-cellulose and alginic acid, cellulose, microcrystalline cellulose, insoluble starch and microcrystalline starch.

. . . 38, wherein said water-insoluble carrier is ethylcellulose, said water-insoluble hydrophilic particulate is calcium pectinate, and said enteric coating is a **methacrylic acid** /methylmethacrylate or ethylacrylate anionic copolymer based on i) **methacrylic acid** and methylmethacrylate or ii) on **methacrylic acid** and ethylacrylate, wherein the ratio of free carboxyl groups to the ester groups is approximately 1:1.

L9 ANSWER 2 OF 3 USPATFULL

AB Compositions and methods for the transdermal delivery of active agents up to a period of seven days or more at substantially a zero-order release rate comprising a pharmaceutically acceptable adhesive matrix and a polymeric plastic material that provides a release rate regulating effect on the active agents.

AN 2002:8068 USPATFULL

TI Compositions and methods to effect the release profile in the transdermal administration of active agents

IN Kanios, David, Miami, FL, UNITED STATES

PI US 2002004065 A1 20020110

AI US 2001-765932 A1 20010119 (9)

PRAI US 2000-177103P 20000120 (60)
DT Utility
FS APPLICATION
LREP Noven Pharmaceuticals, Inc., 11960 S.W. 144th Street, Miami, FL, 33186
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 6 Drawing Page(s)
LN.CNT 2059
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD [0046] A crystallization inhibitor or solubility enhancer may also be employed in the invention, for example polyvinylpyrrolidone polymers, **polyethylene oxide**, polyacrylic acid, polyvinyl alcohol, **silicone dioxide**, silica, celluloses and cellulose derivatives such as hydroxymethyl cellulose, hydroxypropyl cellulose, gelatins, gums, starches, dextrins and dextrans, sterols, bile acids. . .

DETD . . . Nifedipine, Nifenalol, Nilvadipine, Nipradilol, Nisoldipine, Nitroglycerin, Oxprenolol, Oxyfedrine, Ozagrel, Penbutolol, Pentaerythritol Tetranitrate, Pindolol, Pronethalol, Propranolol, Sotalol, Terodiline, Timolol, Toliprolol and **Verapamil**.

DETD . . . Nifenalol, Oxprenolol, Penbutolol, Pindolol, Pirmenol, Practolol, Prajmaline, Procainamide Hydrochloride, Pronethalol, Propafenone, Propranolol, Pyrinoline, Quinidine Sulfate, Quinidine, Sotalol, Talinolol, Timolol, Tocainide, **Verapamil**, Viquidil and Xibenolol.

DETD [0256] Arylalkylamines such as Bepridil, Ditiazem, Fendiline, Gallopanil, Prenylamine, Terodiline and **verapamil**;

DETD [0359] The acrylic polymers useful in practicing the invention are polymers of one or more monomers of **acrylic acids** and other copolymerizable monomers. The acrylic polymers also include copolymers of alkyl acrylates and/or methacrylates and/or copolymerizable secondary monomers or. . .

DETD [0360] Acrylate monomers which can be used include **acrylic acid**, **methacrylic acid**, butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, 2-ethylbutyl acrylate, 2-ethylbutyl acrylate, 2-ethylbutyl methacrylate, isooctyl acrylate, isooctyl methacrylate, 2-ethylhexyl acrylate,. . .

DETD [0361] Functional monomers, copolymerizable with the above alkyl acrylates or methacrylates, which can be used include **acrylic acid**, **methacrylic acid**, maleic acid, maleic anhydride, hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamide, dimethylacrylamide, acrylonitrile, dimethylaminoethyl acrylate, dimethylaminoethyl methacrylate, tert-butylaminoethyl acrylate, tert-butylaminoethyl methacrylate, methoxyethyl. . .

DETD [0367] Suitable co-solvents include polyhydric alcohols, which include glycols, triols and polyols such as ethylene glycol, diethylene glycol, **propylene glycol**, dipropylene glycol, trimethylene glycol, butylene glycol, **polyethylene glycol**, hexylene glycol, polyoxethylene, glycerin, trimethylpropane, sorbitol, polyvinylpyrrolidone, and the like.

DETD . . . monhydric alcohols such as ethyl, isopropyl, butyl and benzyl alcohols; or dihydric alcohols such as ethylene glycol, diethylene glycol, or **propylene glycol** dipropylene glycol and trimethylene glycol; or polyhydric alcohols such as glycerin, sorbitol and **polyethylene glycol**, which enhance drug solubility; **polyethylene glycol** ethers of aliphatic alcohols (such as cetyl, lauryl, oleyl and stearly) including polyoxyethylene (4) lauryl ether, polyoxyethylene (2) oleyl ether. .

L9 ANSWER 3 OF 3 USPATFULL

AB A controlled release pharmaceutical preparation comprising a core containing a medicinal compound and a coating layer containing a water-repellent salt and a water-insoluble and slightly water-permeable acrylic polymer having trimethylammoniumethyl group. Said preparation releases a medicinal compound in a sigmoid type dissolution pattern irrespective of the PH of a dissolution medium.

AN 92:65812 USPATFULL

TI Controlled release pharmaceutical preparation

IN Noda, Kazuo, Takarazuka, Japan
Kobayashi, Masao, Kyoto, Japan
Osawa, Takashi, Toyonaka, Japan
Ishikawa, Shigeyuki, Mino, Japan

PA Tanabe Seiyaku Co., Ltd., Osaka, Japan (non-U.S. corporation)

PI US 5137733 19920811
AI US 1991-723031 19910628 (7)
PRAI JP 1990-171762 19900628
DT Utility
FS Granted
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Spear, James
LREP Browdy and Neimark
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 534
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . surrounds said core. If desired, another coating layer of at least one material selected from the group consisting of ethylcellulose, **hydroxypropylcellulose** and a medicinal compound may be provided around said coating layer in the constrolled release pharmaceutical preparation of the present. . .

DETD In the present invention, a polymer of **acrylic acid**, methyl acrylate, ethyl acrylate, **methacrylic acid**, methyl methacrylate, ethyl methacrylate or the like, which has trimethylammoniumethyl group in the molecule, may be used as a water-insoluble. . .

DETD As ethylcellulose or **hydroxypropylcellulose** which is a material of another coating layer provided around the coating layer of an acrylic polymer, for instance, ethylcellulose containing about 46.5 to about 51.0% of ethoxy group, **hydroxypropylcellulose** containing about 53.4 to about 77.5% of hydroxypropoxy group or the like can be suitably used.

DETD . . . medicinal compound to be contained in the core is not particularly limited. For instance, calcium antagonists such as diltiazem hydrochloride, **verapamil** hydrochloride, nicardipine, nitrendipine and nimodipine, antiasthmatic agents such as theophylline and trimetaquinol, water soluble vitamins, antibiotics, antimalignantumor agents, antipyretic analgesics,. . .

DETD . . . the like. Examples of binders are polyvinylalcohol, polyacrylic acid, polymethacrylic acid, polyvinylpyrrolidone, glucose, sucrose, lactose, maltose, sorbitol, mannitol, hydroxyethylcellulose, hydroxypropylmethylcellulose, **hydroxypropylcellulose**, macrogols, arabic gum, gelatin, agar, starch and the like. Examples of lubricants are **stearic acid**, talc and the like. Examples of aggregation-preventing agents are the above-mentioned lubricants, **silicone dioxide**, colloidal **silicone dioxide** and the like. Examples of

solubilizers for medicinal compounds are organic acids such as fumaric acid, succinic acid and malic. . .

DETD . . . an apparatus by means of air pressure, they are spray-coated with an aqueous dispersion of a water-repellent salt and an **acrylic acid** polymer at an adequate rate from the nozzle of the spray-gun.

DETD . . . a plasticizer, a coloring agent and the like may be contained in the dispersion. As a plasticizer, for instance, triacetin, **triethyl citrate**, acetyltributyl citrate, diethyl phthalate, polyethyleneglycol, polysorbate or the like can be suitably used. The amount of the plasticizer to be. . .

DETD . . . the present invention wherein another coating layer made of at least one material selected from the group consisting of ethylcellulose, **hydroxypropylcellulose** and a medicinal compound is provided around the coating layer containing a water-repellent salt and a water-insoluble and slightly water-permeable. . .

DETD For example, in case of coating with ethylcellulose or **hydroxypropylcellulose**, the solution prepared by dissolving ethylcellulose or **hydroxypropylcellulose** in water, methanol, ethanol, acetone or a mixed solvent thereof to be the concentration of about 0.5 to about 10%,. . .

DETD . . . preparation of the present invention wherein the coating layer of a slightly water-permeable acrylic polymer is further coated with ethylcellulose, **hydroxypropylcellulose** or the like, has a following advantage. That is, because the dissolution rate of a medicinal compound after a lag. . .

DETD . . . adjusting the amounts of the medicinal compound layer and an acrylic polymer layer or providing an another coating layer of **hydroxypropylcellulose** or the like around the layer of a medicinal compound. Therefore, the pharmaceutical preparation of the present invention has an. . .

DETD . . . was spray-coated with a solution containing 30 parts of Eudragit RS, 10 parts of calcium stearate and 3 parts of **triethyl citrate** to obtain various controlled release pharmaceutical preparations (a) to (e) containing diltiazem hydrochloride, which differ from each other in the. . .

DETD . . . (a copolymer of ethyl acrylate, methyl methacrylate and .beta.-acryloyloxyethyltrimethylammonium chloride, from Rohm Pharma, Germany) (84 g), calcium stearate (28 g), **triethyl citrate** (8 g), ethanol (160 g) and water (320 g). After coating, the granule was dried by heating at 60.degree. C.. . .

DETD . . . the same manner as in Example 1 except that a mixture of Eudragit RS (112 g), calcium stearate (37 g), **triethyl citrate** (11 g), ethanol (210 g) and water (430 g) was used as a coating solution to obtain a controlled release. . .

DETD . . . the same manner as in Example 1 except that a mixture of Eudragit RS (140 g), calcium stearate (47 g), **triethyl citrate** (14 g), ethanol (267 g) and water (533 g) was used as a coating solution to obtain a controlled release. . .

DETD . . . carried out in the same manner as in Example 3 except that tributyl acetylcitrate (14 g) was used instead of **triethyl citrate** as a plasticizer to obtain a controlled release pharmaceutical preparation containing diltiazem hydrochloride (yield: 1.2 kg).

DETD . . . as in Example 3 was put into CF apparatus and spray-coated with a coating solution consisting of ethylcellulose (9.5 g), **hydroxypropylcellulose** (0.5 g), ethanol (59 g) and water (32 g). Then the preparation was dried at 60.degree. C. for 16 hours. . .

DETD . . . Freund Industrial Co. Ltd., Japan) and spray-coated with a solution consisting of Eudragit RS (224 g), calcium stearate (74 g), **triethyl citrate** (22 g), ethanol (420 g) and water (860 g). Then the tablets were dried by heating at 60.degree. C. for.

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DETD . . . was put into CF apparatus and spray-coated with a solution consisiting of Eudragit RS (105 g), calcium stearate (35 g), **triethyl citrate** (11 g), ethanol (200 g) and water (400 g). Then the granule was dried by heating at 60.degree. C. for. .

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DETD . . . was put into CF apparatus and spray-coated with a solution consisiting of Eudragit RS (279 g), calcium stearate (93 g), **triethyl citrate** (28 g), ethanol (533 g) and water (1067 g). After coating, the granule was dried by heating at 60.degree. C.. . .

CLM What is claimed is:

. . . of claim 1, wherein another coating layer made of at least one material selected from the group consisting of ethylcellulose, **hydroxypropylcellulose** and a medicinal compound is provided around the coating layer on the surface of the core.

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